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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,604	02/12/2004	Nobuyoshi Shimizu	0652.2110001/JUK/KPQ	3951

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,604	SHIMIZU ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-79* is/are pending in the application.

4a) Of the above claim(s) *43-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78 and 79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☑ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☑ Certified copies of the priority documents have been received in Application No. 09/601,844

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III, claims 78-79 in the reply filed on 11-21-06 is acknowledged. The traversal is on the ground(s) that the search of Groups I, II, and III would not impose a serious burden upon the examiner because a search concerning the patentability of the invention of one group is likely to uncover art of interest into the other group. This is not found persuasive because a search for a point mutation (as set forth in the claims of group III) at one particular nucleotide would not be coextensive with a search that would identify smaller nucleotide sequences that don't overlap with the region of the point mutation recited in group III. Moreover, the invention set forth in group II comprises a search for partial or complete deletions, not for substitutions that would result in the change of an amino acid. Therefore, the search of invention group III would not be coextensive with that of invention group II. Moreover, the search of invention group I, which comprises the use of a plurality of short primer sequences, would not be coextensive with the search of group II or III. Moreover, as stated in the prior office Action, the review of multiple search reports for each of the sequences recited in claim 62 would also constitute an examination burden since the search of each of these sequences would potentially produce multiple pages of search results that would have to be properly reviewed and considered. The search of any one fragment, primer, partial sequence or variant is not a search of any other because the searches are not co-extensive and would not reveal all relevant art to the patentably

distinct inventions. The MPEP does not require that multiples sequences be examined in a single application.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 43-77 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11-21-06.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 78-79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The scope of the instant invention comprises wherein the identification of a single point mutation at nucleotide position 366 of SEQ ID NO: 1 or SEQ ID NO: 2 in any human would produce a determination of a predisposition to Parkinson's disease. It is noted that the claims does not require that the point mutation be present in both strands of the DNA present in a human. Moreover, the instant claims are drawn to wherein the point mutation may comprise wherein the "C" at position 366 is changed from C to A, G, or T, or to even wherein there is a deletion at position 366. Additionally, the scope of the claims encompasses wherein the human patient, is any human subject, including all ethnic backgrounds, age backgrounds, as well as both male and female.

The nature of the present invention requires knowledge of a relationship between the presence of a single nucleotide polymorphism in the Parkin gene (SEQ ID NO: 1 or 3) and the increased risk to develop Parkinson's disease.

Parkinson's disease (PD) is not regarded as a single disease and there is a high level of difficulty in distinguishing PD from other forms of parkinsonism, see for example Tolosa et al. (2006), which states:

> "Parkinson's disease is a progressive neurological disorder characterised by tremor, rigidity, and slowness of movements, and is associated with progressive neuronal loss of the substantia nigra and other brain structures. Non-motor features, such as dementia and dysautonomia, occur frequently, especially in advanced stages of disease. Parkinson's disease is not regarded as a single disease entity and the term does not necessarily mean the same for all clinicians and researchers. Some use the term as a strictly clinical diagnosis and might accept different pathological substrates underlying the syndrome. Others will use the term only for those cases of idiopathic parkinsonism associated with Lewy body inclusions in the nigra cells and in cells in other brain regions. Here we use the term Parkinson's disease to refer to a clinical condition—progressive parkinsonism of undetermined cause without features suggestive of an alternative diagnosis responding to dopaminergic treatment—associated with depletion of brainstem neurons and with Lewy body inclusions in some of the remaining nerve cells.
>
> Although a diagnosis of Parkinson's disease, as defined above, can be a straightforward clinical exercise in patients with typical presentations of cardinal signs and excellent response to levodopa treatment, the differential diagnosis versus other forms of parkinsonism can be challenging, especially early in the disease when signs and symptoms of different forms of parkinsonism have greater overlap. Error rates in clinicopathological series have been as high as 24% even though most of the patients in these studies had been treated by movement-disorder specialists." (see page 75)."

Tolosa et al. concluded that "[D]espite advances in imaging and genetics of parkinsonian disorders the diagnosis of Parkinson's disease remains a primarily clinical exercise. However, the clinical diagnostic uncertainty is high at initial presentation and up to 30% of patients initially diagnosed as having the disease are clinically reclassified, even in specialized units." (see page 82, conclusion).

Additionally, it is clear from the state of the art that both parkinsonism and Parkinson's disease are difficult to diagnose. For example, Meara et al., taught that out of 402 subjects with presumed Parkinson's disease, a definite diagnosis of PD was only made in 213 (53%) of the cases. Additionally, parkinsonism was confirmed in only 299 (74%) of the subjects, and of these 299, 213 or 71% of the individuals with

parkinsonism was judged to be clinically probable Parkinson's disease. (see Results section on page 100).

According to the specification as filed, in regards to the R366W polymorphism, although the expected frequencies of the three genotypes were exactly the same between the PD patients and the control, the allele frequencies of the Arginine to Tryptophan polymorphism at nucleotide position 366 (CGG→ TGG) differed significantly between PD patients and the control subjects (see pages 42, paragraph [0142]). Moreover, the specification stated that the allele frequency in the PD patients was significantly lower compared to that of the control. Based upon these observations Applicants concluded that since the allele frequency of R366W was extremely low in PD patients, this result suggested that the allele constitutes a protective factor against PD that inhibits onset of PD.

Applicant's conclusion that the frequency of this allele constitutes a protective factor against PD is not supported by any experimental data, since individuals having the R366W polymorphism in the PD group still had the disease (see Table 7). Furthermore, the instant claims are drawn to a method for diagnosing a predisposition of a human subject for Parkinson's disease by observing the presence of an Arg to Trp mutation at position 366, namely the R366W polymorphism. However, according to Applicant's specification this polymorphism "functions as a protective factor against PD." Applicant's specification appears to contradict the method recited in claims 78-79.

Furthermore, Sinha et al. provided a study further elucidating the role of the *parkin* gene mutations and the development of Parkinson's disease. The R366W

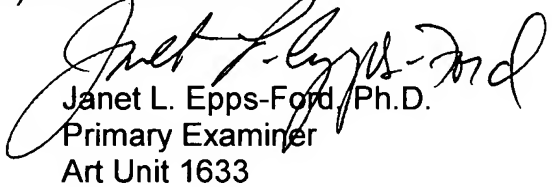
polymorphism was studied, see Table 1, and Table 2, and it was concluded that there was no difference in the allele or genotype frequency among PD patients and controls (see page 344, paragraphs 1-2). The findings of Sinha et al. did not support a major role of *parkin* mutations in the majority of cases of Parkinson's disease (see last paragraph, page 345).

Due to the high level of unpredictability associated with making an accurate diagnosis of Parkinson's disease, the limited guidance in the specification as filed, and the apparent contradiction with the results observed in Sinha et al., the skilled artisan would not have been able to practice the full scope of the claimed invention without undue experimentation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Janet L. Epps-Ford, Ph.D.
Primary Examiner
Art Unit 1633

JLE